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Asymmetric synthesis of trifluoromethyl-piperidine based γ-amino acids and of trifluoromethyl-indolizidines

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ABSTRACT

The asymmetric synthesis of trifluoromethyl-piperidine-based γ-aminoacids and of indolizidines bearing a trifluoromethyl group is reported. These rarely described compounds are prepared in a highly enantio-enriched form employing as key step an intramolecular Mannich type process, involving an enantiopure Tfm-aminoketal and ethyl oxobutenoate as aldehyde partner. Used strategy together with obtained compounds allows the access to a wide range of Tfm-*N*-(poly)heterocycles, structures of obvious interest for the research of new bioactive drugs.

1. Introduction

Due to the therapeutic benefits issued from the incorporation of fluorine atom(s) into the skeleton of bioactive molecules, fluoro-organic chemistry became a major research field for pharmaceutical industry [1]. As a consequence, organo-fluorine chemistry makes the object of continuous and intensive research efforts [2]. Meanwhile, some areas remain poorly explored, as the stereoselective synthesis of saturated *N*-heterocycles bearing a trifluoromethyl (CF_3) group, and, among these challenging targets [3], the case of CF_3-piperidines. Effectively, despite the high potential of the piperidine ring system for drug discovery [4], enantio-enriched trifluoromethylated analogues have been very rarely described [5,6].

In this context, we have communicated [7] a highly stereoselective access to enantiopure α-CF_3-piperidines relying on an intramolecular Mannich strategy [8] for the key cyclization step (Scheme 1).

In order to explore the synthetic potential of this approach, we decided to apply it to the elaboration of original fluorinated (poly)heterocyclic frameworks. Because they represent an undeniable interest for the research of new bioactive structures, CF_3-piperidine-based γ-amino acids **1** and indolizidines **2** were targeted (Fig. 1).

2. Results and discussion

The asymmetric synthesis of the trifluoromethylated analogue **1** of γ-aminobutyric acid (GABA) was considered at first. GABA is the main inhibitory neurotransmitter in the central nervous system and several important neurological or psychiatric disorders are associated with its deficiency. Unfortunately, inability of GABA to cross the blood-brain barrier makes its general administration (oral or intravenous) vain for the treatment of such illness. As a consequence, research toward more lipophilic and active analogues received considerable attention. Nevertheless, among the multiple studies engaged to solve this problem [9], a very few described the enantioselective synthesis of structures possessing a piperidine backbone. Furthermore and as far as we know, only one [10] CF_3-piperidine bearing also a γ-amino acid function (achiral compound) has been described [11].

Because the intramolecular Mannich route seemed appropriate for the stereoselective construction of piperidine-based γ-amino acids bearing a lipophilic CF_3 group, their synthesis was engaged.

As already reported [7] enantiopure [12] antipodes of β-aminoketal key synthon **3** were easily prepared in a conventional three steps sequence from fluorinated enone **4** [13] *via* intermediates **5**–**6**, but also in a highly diastereoselective manner [14]

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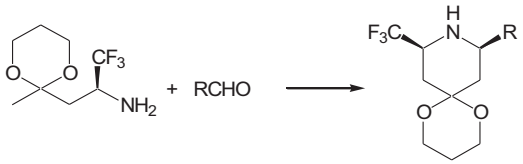


Scheme 1. A stereoselective access to Tfm-piperidines.

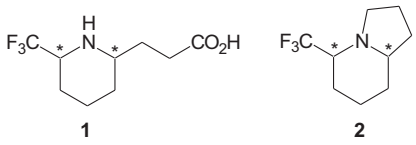


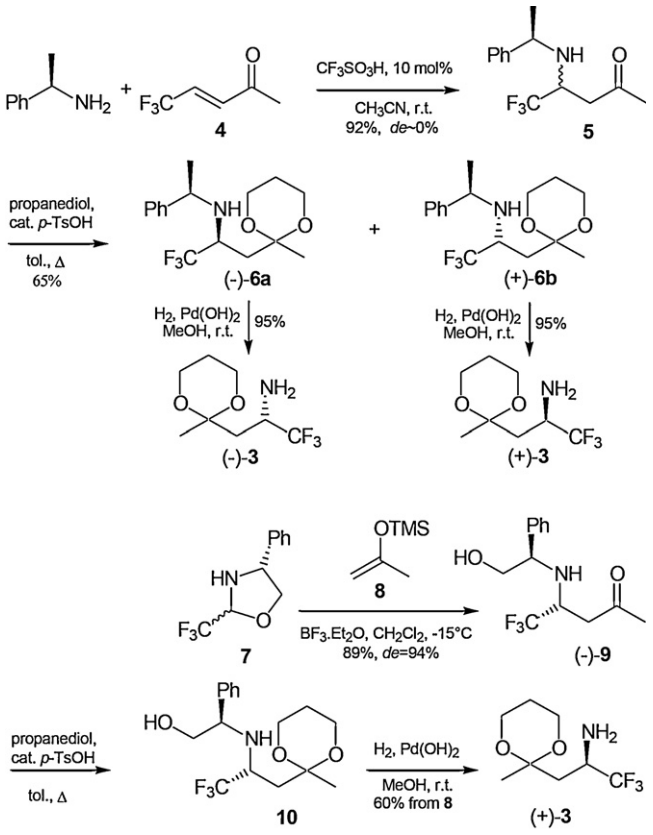
Fig. 1. Targeted Tfm-*N*-heterocycles.

using a "Fox" (chiral fluorinated oxazolidine) methodology [15] involving oxazolidine **7** [16] and enoxysilane **8** (Scheme 2).

Next was the key cyclization step. Thus, reaction of aminoketal (+)-**3** with ethyl (*E*)-oxobutenoate was conducted under our classical acidic intramolecular Mannich process conditions [8]. An interesting diastereoselectivity was achieved (*de* = 85% from GC/MS of the crude). The expected [8] *cis*-2,6-disubstituted CF_3-piperidine (+)-**11** was isolated in 68% yield (Scheme 3) with an high enantiopurity (*ee* = 96% from chiral HPLC, in comparison with the racemic material). Our first free azacyclic γ-amino acid (±)-**12** was then easily obtained from racemic **11**. A simple palladium hydroxide catalyzed saturation of the double bond was followed by saponification of the resulting ester (±)-**13**. Acidic work-up then migration of the formed hydrochloride through an ion-exchange resin furnished (±)-**12** (87% overall yield).

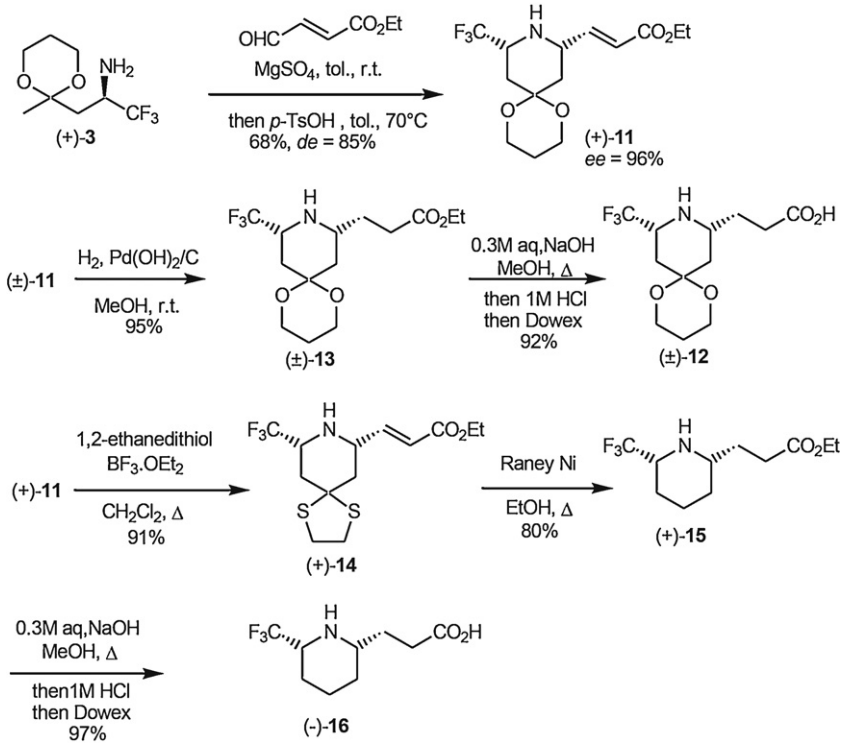
With enantio-enriched piperidine (+)-**11** in hands, we had the opportunity to propose – to our knowledge – the first asymmetric synthesis of a CF_3-piperidine-based GABA analogue (Scheme 3).

As summarized in Scheme 3, this was efficiently achieved in three steps from piperidine (+)-**11**. The dioxane moiety of (+)-**11**



Scheme 2. Asymmetric synthesis of keto-protected Tfm-aminobutanone.

was transformed into dithiolane (+)-**14** which, upon hydrogenation/hydrogenolysis using excess of Raney nickel in ethanol at reflux furnished the cyclic γ-aminoester (+)-**15**. Finally, saponification of the latter followed by purification on a Dowex® resin

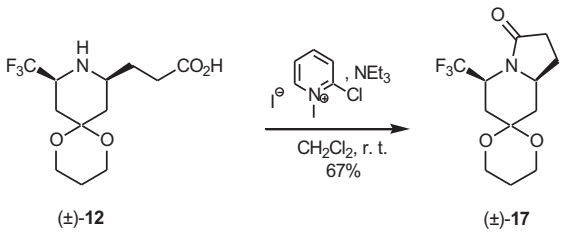


Scheme 3. Stereoselective preparation of Tfm-piperidine-based γ-amino acids.

liberated the targeted heterocycle (−)-**16** in a 71% total isolated yield. As observed – and as already proven [7,17] with other related series – that these reaction conditions did not provoke any epimerization so no racemization, we assume that CF_3-azacyclic γ-amino acid (−)-**16** such synthetized presents an excellent enantiomeric purity (*ee* = 96%). Moreover, we assume also that, with poly-functionalized intermediates such as piperidine **11**, the results described herein open a stereoselective entry to a wide range of new lipophilic and constrained GABA analogues.

Next was the valuation of this intramolecular Mannich methodology toward the construction of trifluoromethylated indolizidine-type systems. Indeed, although this bicyclic framework is commonly encountered in Nature and even if it has been outlined [18] that the incorporation of a CF_3 group in an alkaloid skeleton may serve the development of new bio-active compounds, the selective synthesis of mono CF_3 indolizidines remains a *quasi* virginal research domain. Effectively, we were able to find in the literature only two CF_3-indolizidines [5d,19] and only five CF_3-indolizidinones [18,19]. It has to be noticed that among these scarce compounds, only one indolizidine has been obtained in a non-racemic form (trifluoromethylated analogue of the well known alkaloid monomorine [5d]). For our own, we thought that enantiopure indolizin(on)es would be quite rapidly attainable from our piperidine-based γ-aminoesters or derived amino acids (Scheme 4).

First direct cyclization attempts concerned product **13**, but gave disappointing results. Whatever the reaction conditions involved – use of an organic base or of a Lewis acid – the formation of the expected heterobicycle **17** could not be observed, starting material remaining intact. To circumvent this difficulty, the lactamization of amino acid **12** was taken into account. Thus, treatment of (±)-**12** with Mukaiyama's reagent [20], at room temperature in dichloromethane in the presence of triethylamine, resulted this time in the clean formation of indolizidinone (±)-**17**, the first trifluoromethyl aza-bicyclic γ-lactam (67% isolated yield,



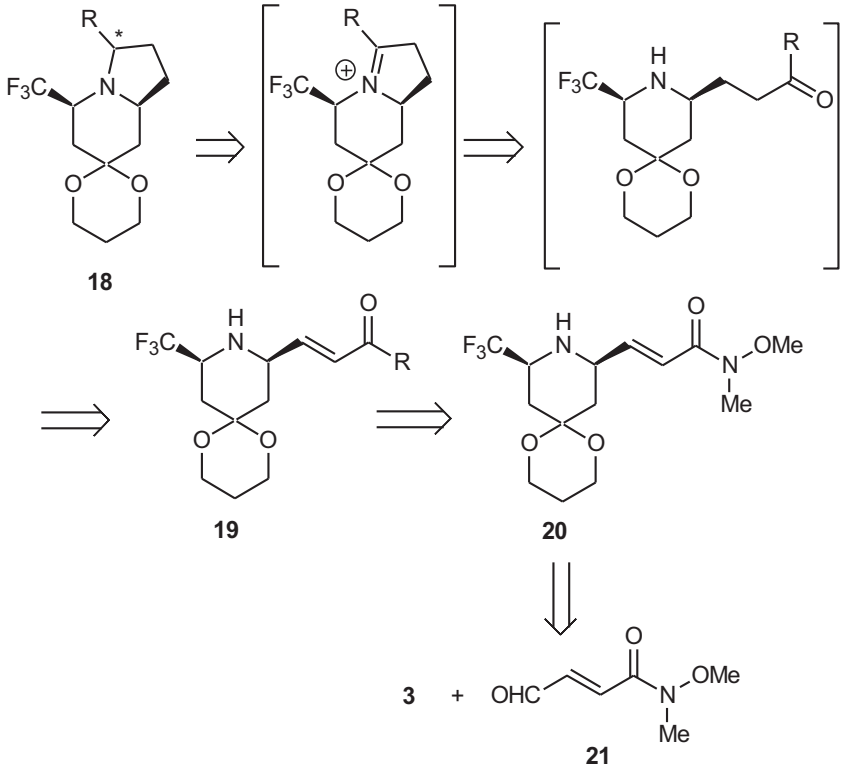
Scheme 4. Synthesis of a Tfm-indolizidinone.

Scheme 4). The corresponding indolizidine would be at this stage easily obtained from **17** by lithium aluminum hydride or borane mediated deoxygenation of the amido group. Anyway, as we wished to develop a more concise and in particular a more general pathway to this molecular scaffold, allowing the selective introduction of a supplementary stereogenic center, an alternative route was foreseen (Scheme 5).

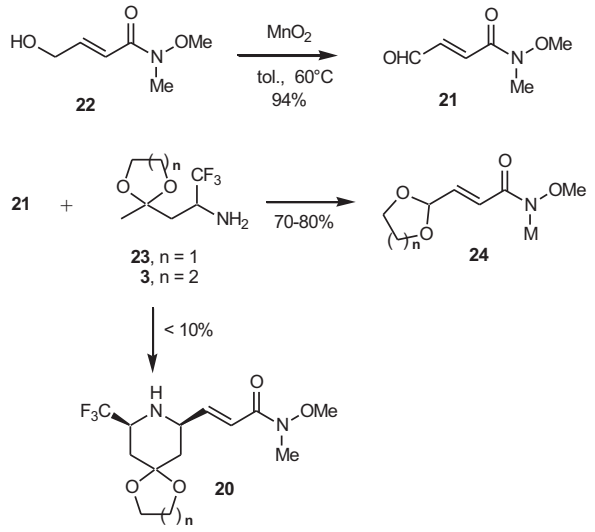
We reasoned that trifluoromethyl indolizidines **18** would directly arise from simple hydrogenation of enone **19** through an double bond saturation – intramolecular reductive amination cascade [21]. Access to key unsaturated ketones **19** appeared conceivable by the use of Grignard reagents addition onto Weinreb amide **20**, intramolecular Mannich reaction adduct of amine **3** and functionalized aldehyde **21**.

Synthesis of enal **21** was envisaged by oxidation of allylic alcohol **22**, available in two steps from maleimide, according to Jacobi's procedure [22] (Scheme 6).

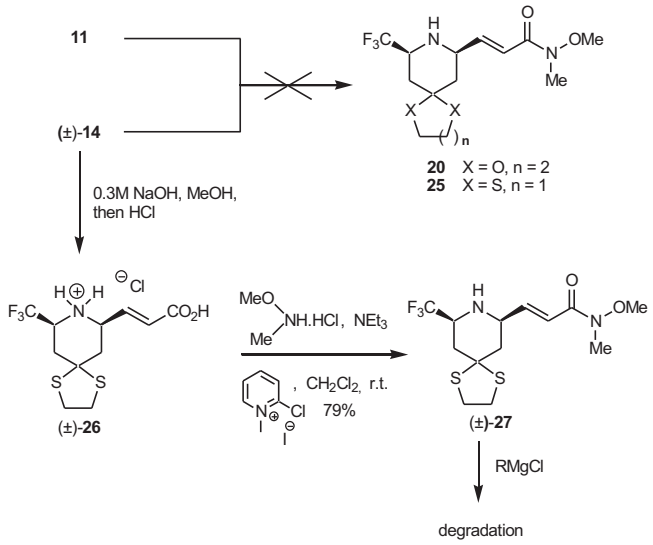
Treatment of alcohol **22** with manganese dioxide at 60 °C in toluene furnished in 94% yield aldehyde **21**. Next was its employment in our Mannich-type process. Unexpectedly, all cyclization trials conducted either with amines **3** or **23**, failed to give piperidine **20** (<10%, GC/MS) efficiently, but yielded in a reproducible manner the transacetalization products **24**. This very



Scheme 5. Retrosynthetic pathway to Tfm-indolizidines.



Scheme 6.



Scheme 7.

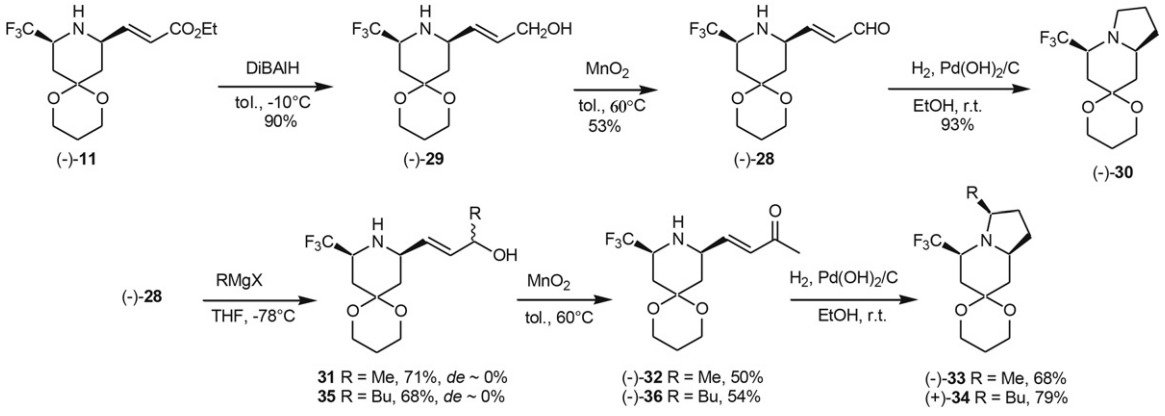
disappointing result forced us to revisit our synthetic scheme. For this reason, piperidines **11** and **14** were submitted to Weinreb's procedure [23] in order to prepare the corresponding amides **20** and **25**, but with no more success, due to their degradation during the reaction (Scheme 7).

Finally, saponification of ester **14** followed by treatment of the resulting acid **26** with *N,O*-dimethylhydroxylamine hydrochloride, in the presence of triethylamine and of Mukaiyama's coupling reagent, allowed us to get the Weinreb amide **27**. Unluckily, using various Grignard reagents under different reaction conditions, it has never been possible to obtain cleanly the desired dithio analogues of ketones **19**, due to extensive degradation. In our minds, these last and surprising failures condemned the "Weinreb route" to sink into oblivion.

Anyway, because transformation of an α,β-unsaturated ester into the corresponding enal or alkyl enone doesn't constitute a major problem, we redefined a synthetic scheme starting from CF_3 piperidine (−)-**11**, as shown in Scheme 8. Reduction of (−)-**11** using strictly one equivalent of diisobutyl aluminum hydride at low temperature (−78 °C) led to a statistical mixture of unreacted ester, parent aldehyde (−)-**28** and alcohol (−)-**29**. It appeared so preferable to completely reduce the ester function with an excess of reducing agent. Allylic alcohol (−)-**29** thus conveniently prepared (90% yield) was subsequently converted into aldehyde (−)-**28** by MnO_2 mediated oxidation. Catalytic hydrogenation of (−)-**28** using Pearlman's reagent at room temperature in ethanol then furnished expediently the wished CF_3-indolizidine (−)-**30** in a 40% overall yield from (−)-**11**.

In order to prepare related trifluoromethylated polycyclic systems but incorporating a supplementary asymmetric center, a similar pathway was considered (Scheme 8).

Addition of methyl magnesium bromide on aldehyde (−)-**28**, carried out at -78 °C in tetrahydrofuran, led in a 71% yield to an inseparable mixture of epimers **31**, that was oxidized with MnO_2 to give the corresponding enone (−)-**32**. Palladium hydroxide catalyzed hydrogenation of (−)-**32** then afforded, *highly stereoselectively*, (only one stereoisomer from GC/MS and ^{1}H NMR data of the crude reaction mixture) the three stereogenic centers-containing CF_3-indolizidine (−)-**33** (24% overall yield from piperidine **28**). Applying the same reaction sequence, using butyl magnesium chloride instead of methyl magnesium bromide, a new CF_3-indolizidine (+)-**34** – a trifluoro-analogue enantiomer of alkaloid monomorine [24] – was formed as the sole detectable stereoisomer, in three steps and in 29% overall yield from enal (−)-**28**. Relative *all-cis* and therefore absolute configuration of the newly created stereogenic carbons, represented in Scheme 8, were assigned in total respect with unambiguous literature data [5d,21]. As it was established that in these series experimental conditions entailed no epimerization and in consequence no racemization (see above), we can consider that CF_3-indolizidines described here possess an identical enantio-purity to those of starting piperidine **11** (*ee* = 96%).



Scheme 8. Preparation of highly enantio-enriched Tfm-indolizidines.

3. Conclusion

We have reported herein the highly stereoselective syntheses of original trifluoromethylated saturated *N*-(poly)heterocycles. These recognized challenging – and in consequence very scarcely described compounds – were prepared in a straightforward fashion. A maximum of six steps starting from a readily available enantiopure α-CF_3-aminoketal chiron was necessary. An intramolecular Mannich-type process constituted the key cyclization step. Simple synthetic methods, associated with polyfunctional CF_3-structures isolated – possessing notably a latent keto function susceptible to endure multiple transformations – make, we think, this work of great interest for research of new fluorinated bioactive products.

4. Experimental

4.1. General

Solvents were distilled prior to use. Other reagents were used as received. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotatory evaporator. Thin layer chromatography was performed on TLC pre-coated aluminum backed silica plates Kieselgel 60 F_{254} (Merck) or glass backed silica Duracil 25 UV_{254} (Macherey Nagel). Spots were visualized using UV light (254 nm) before using an ethanolic solution of phosphomolybdic acid (heating). Enantiomeric excess determination of compound **11** was carried out by HPLC using a Chiralcel OB column (hexane/isopranol, 90/10, v/v, 350 psi). Purifications by column chromatography were carried out on silica gel (70–230 mesh). Purifications on resin were carried out on an ion-exchange resin Dowex® 50WX8-100, regenerated with a solution of 1 N HCl and washed with distilled water. Melting points were measured by a Reichert plate-heating microscope. Optical rotations were measured on a Jasco DIP-370 polarimeter at the wavelength of sodium D ray (λ = 589 nm). The Infra-Red spectra were recorded on a Perkin Elmer Paragon 500 FTIR spectrophotometer in the form of film between NaCl plates (liquids), or in the form of pellets of KBr (solids). The characteristic band positions ν_{max} are expressed in cm^{-1}. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometer at 400.13, 100.61 and 376.50 MHz respectively. Chemical shifts δ are reported in ppm relative to solvent residual signals (^1H and ^{13}C) or to hexafluorobenzene (^{19}F, $\delta = -164.9$ ppm). The coupling constants *J* are given in Hertz (Hz). Electron Impact Mass Spectra (EI-MS) were obtained on a spectrometer Hewlett Packard 5989B at 70 eV. High Resolution Electro-Spray Ionization Mass Spectra (HR-ESI-MS) were obtained from the "Centre Régional de Mesures Physiques de l'Université Blaise Pascal". GC/MS analysis conditions used for diastereomeric excess determination were as follows: column: UB 1701 (14% cyanopropylphenyl)-methylpolysiloxane; injector temperature: 250 °C; oven temperature: 50 °C for 2 min then heating 50 °C/min until 290 °C.

The abbreviations used for signal descriptions are as:

s: singlet, br s: broad singlet, d: doublet, dd: doublet of doublets, ddd: doublet of doublet of doublets, dt: doublet of triplets, dq: doublet of quartets, t: triplet, tt: triplet of triplets, q: quartet, Q: quintet, m: multiplet, ax: axial, eq: equatorial.

4.1.1. (+)-5,5,5-Trifluoro-4-[(R)-1-phenylethylamino] pentan-2-one (**5**)

To a stirred solution of (*R*)-(+)-α-methylbenzylamine (11.07 mL, 91 mmol) and trifluoromethane sulfonic acid (514 μL, 3.4 mmol) in acetonitrile (150 mL) was added, trans-5,5,5-trifluoropent-3-en-2-one [13] (8.00 g, 58 mmol) and the reaction mixture was stirred at room temperature for 1 h. Saturated $NaHCO_3$ (25 mL) was added before extraction with ethyl acetate (3× 150 mL) and the combined organic extracts were dried over Na_2SO_4, filtered then concentrated under reduced pressure. Silica gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave title compound **5** (1/1 inseparable mixture of diastereoisomers, 13.8 g, yield: 92%) as a pale yellow oil. R_f: 0.65 (ethyl acetate/cyclohexane = 1/3). δ_H (400 MHz, $CDCl_3$) 7.30 (m, 5H, H-Ar); 4.08 (q, *J* = 6.5 Hz, 0.5H, 1st dia); 4.00 (q, *J* = 6.5 Hz, 0.5H, 2nd dia), 3.68 (m, 0.5H, 1st dia), 3.42 (m, 0.5H, 2nd dia), 2.76–2.44 (m, 2H), 2.16 (s, 1.5H, 1st dia), 2.02 (s, 1.5H, 2nd dia), 1.60 (br s, 1H, NH), 1.34 (d, *J* = 6.5 Hz, 1.5H, 1st dia), 1.32 (d, *J* = 6.5 Hz, 1.5H, 2nd dia). δ_C (100 MHz, $CDCl_3$) 205.7, 140.3, 128.6, 128.2, 127.4, 126.3 (q, J_{C-F} = 283 Hz, CF_3), 67.2, 62.2, 53.5 (q, J_{C-F} = 29 Hz), 43.0, 30.6. δ_F (376 MHz, $CDCl_3$) −77.9 (1st dia), −77.0 (2nd dia). EI-MS (70 eV) *m/z* 259 (M^+, 1), 244 (100), 200 (25), 186 (30), 159 (40), 120 (50), 105 (90), 77 (40), 43 (50). HR-ESI-MS calculated for $C_{13}H_{17}NOF_3$ $(M+H)^+$: 260.1262, found 260.1258.

4.1.2. (2S)-(−)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)-N-[(R)-1-phenylethyl]propan-2-amine (**6a**)

In a flask fitted with a Dean–Stark apparatus, was added to a solution of ketone **5** (12 g, 46.3 mmol) in toluene (200 mL), propane-1,3-diol (8.3 mL, 109 mmol) and *p*-TsOH (3.5 g, 18.4 mmol). The resulting mixture was heated at reflux for 5 h, then cooled to room temperature and was treated with 50 mL of a saturated $NaHCO_3$ solution. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3× 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The 2 diastereoisomers were separated by silica gel column chromatography (ethyl acetate/cyclohexane = 1/19) to afford 5.03 g (34%, pale yellow liquid) of (2*R*)-(−)-**6a**, and 4.60 g (31%, pale yellow liquid) of another diastereomer (2*S*)-(+)-**6b**.

Analytical data for **6a**: R_f: 0.55 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = -1.5$ (*c* 1.06, $CHCl_3$). ν_{max} (liquid film) 3357, 2967, 2874, 1245, 115, 1107, 701. δ_H (400 MHz, $CDCl_3$) 7.40–7.20 (m, 5H), 4.05 (m, 3H,), 3.89 (m, 2H), 3.56 (Qd, 1H, *J* = 8 and 1.5 Hz), 2.05 (dd, 1H, *J* = 15 and 1.5 Hz), 1.95 (m, 2H), 1.82 (dd, 1H, *J* = 15 and 8 Hz), 1.52 (s, 3H,), 1.46 (m, 1H), 1.40 (d, 3H, *J* = 6.5 Hz). δ_C (100 MHz, $CDCl_3$) 145.7, 128.2, 126.8, 127.3 (q, J_{C-F} = 280 Hz, CF_3), 98.2, 59.8 (2C), 56.6, 53.7 (q, J_{C-F} = 28 Hz), 40.7, 25.3, 23.1, 19.7. δ_F (376 MHz, $CDCl_3$) −78.0. EI-MS (70 eV) *m/z* 317 (M^+, 2), 302 (60), 258 (45), 244 (65), 200 (30), 186 (35), 120 (35), 105 (100), 101 (80), 77 (20), 43 (40). HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_2$ $(M+H)^+$: 318.1681, found 318.1669.

4.1.3. (2R)-(+)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)-N-[(R)-1-phenylethyl]propan-2-amine (**6b**)

For preparation of the title compound, see Section 4.1.2.

R_f: 0.51 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = +27.5$ (*c* 1.06, $CHCl_3$). ν_{max} (liquid film) 3350, 2973, 2873, 1247, 1150, 1107, 701. δ_H (400 MHz, $CDCl_3$) 7.30 (m, 5H), 3.99 (q, 1H, *J* = 6.5 Hz), 3.87 (m, 2H), 3.71 (m, 2H), 3.28 (m, 1H), 2.40 (br s, 1H, NH), 1.83 (m, 2H), 1.62 (m, 1H), 1.39 (d, 3H, *J* = 6.5 Hz), 1.29 (m, 1H), 1.20 (s, 3H). δ_C (100 MHz, $CDCl_3$) 144.3, 128.3, 127.2, 127.1, 127.1 (q, J_{C-F} = 282 Hz, CF_3), 98.3, 59.6 (2C), 56.6, 53.0 (q, J_{C-F} = 27 Hz,), 40.0, 24.8, 24.1, 18.8. δ_F (376 MHz, $CDCl_3$) −77.6. EI-MS (70 eV) *m/z* 317 (M^+, 1), 302 (60), 258 (45), 244 (65), 200 (30), 186 (35), 120 (70), 105 (100), 101 (80), 77 (20), 43 (40). HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_2$ $(M+H)^+$: 318.1681, found 318.1669.

4.1.4. (4R)-(−)-5,5,5-Trifluoro-4-[(1R)-2-hydroxy-1-phenylethylamino]pentan-2-one (**9**)

To a stirred solution of oxazolidine **7** [16] (1.00 g, 4.6 mmol) in dichloromethane (30 mL) was added isopropenyloxytrimethylsilane (1.15 mL, 10 mmol) and the reaction mixture

was cooled to −15 °C before addition of borontrifluoride diethyl etherate (1.41 mL, 10 mmol). The resulting mixture was stirred at −15 °C for 1 h before addition of 10 mL of saturated $NaHCO_3$. After separation, the aqueous layer was extracted with dichloromethane (3× 30 mL) and the combined organic extracts were dried over sodium sulfate, filtered then concentrated under reduced pressure. Silica gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave ketone **9** (1.12 g, yield: 89%) as a colorless liquid. R_f: 0.15 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = -24.1$ (*c* 0.90, $CHCl_3$). ν_{max} (liquid film): 3421, 3346, 2934, 1719, 1362, 1266, 1165, 1130. δ_H (400 MHz, $CDCl_3$) 7.32 (m, 5H), 4.03 (dd, 1H, *J* = 8 and 4 Hz), 3.81 (m, 1H), 3.75 (dd, 1H, *J* = 11 and 4 Hz), 3.58 (dd, 1H, *J* = 11.5 and 8 Hz), 2.94 (br s, 1H, OH), 2.80 (dd, 1H, *J* = 17.5 and 4 Hz,), 2.70 (dd, 1H, *J* = 17.5 and 8.5 Hz), 2.18 (s, 3H), 1.90 (br s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 205.7, 140.3, 128.6, 128.2, 127.4, 126.3 (q, J_{C-F} = 283 Hz, CF_3), 67.2, 62.2, 53.5 (q, J_{C-F} = 29 Hz), 43.0, 30.6. δ_F (376 MHz, $CDCl_3$) −78.1. EI-MS (70 eV) *m/z*: 244 ($(M-CH_2OH)^+$; 100), 186, 159, 104 (10) 77 (20), 43 (15). HR-ESI-MS calculated for $C_{13}H_{16}F_3NNaO_2$ $(M+Na)^+$: 298.1013, found 298.1018.

4.1.5. (2R)-2-Phenyl-2-[(2R)-1,1,1-trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-ylamino]ethanol (**10**)

In a flask fitted with a Dean–Stark apparatus, was added to a solution of (−)-**9** (915 mg, 3.3 mmol) in benzene (40 mL), propane-1,3-diol (640 μL, 8.25 mmol) and *p*-TsOH (316 mg, 1.6 mmol). The resulting mixture was heated at reflux for 2 h then allowed to cool to room temperature and was treated with a saturated $NaHCO_3$ solution (10 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (3× 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Silica gel column chromatography (ethyl acetate/cyclohexane = 1/3) gave compound **10** (831 mg, yield: 75%), accompanied with a minor unseparable and unidentified impurity (presence certainly of a ketals equilibrium, second ketal formed with the hydroxyl group of the phenylglycinol moiety). R_f: 0.32 (ethyl acetate/cyclohexane = 1/2). δ_H (400 MHz, $CDCl_3$) 7.34 (m, 5H), 4.10–3.46 (m, 8H,), 3.40 (br s, 1H, OH), 2.03 (dd, 1H, *J* = 15 and 2 Hz), 1.99 (m, 1H), 1.87 (dd, 1H, *J* = 15 and 8 Hz), 1.87 (br s, 1H, NH), 1.80 (s, 3H), 1.46 (m, 1H). δ_C (100 MHz, $CDCl_3$) 141.2, 128.6, 128.2, 127.3, 126.8 (q, J_{C-F} = 280 Hz, CF_3), 98.5, 66.7, 63.2, 60.0 (2C), 54.3 (q, J_{C-F} = 28 Hz), 41.7, 25.1, 19.5. δ_F (376 MHz, $CDCl_3$) −79.0. EI-MS (70 eV) *m/z*: 318 ($(M-Me)^+$, 5), 302 (100), 244 (90), 186 (50), 159 (25), 106 (25), 43 (40). HR-ESI-MS calculated for $C_{16}H_{23}F_3NO_3$ $(M+H)^+$: 334.1630, found 334.1615.

4.1.6. (S)-(−)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-amine (**3**)

In an hydrogenation vessel (Parr apparatus) was placed a solution of diastereoisomer **6a** (2.20 g, 6.94 mmol) in methanol (80 mL), then was added 20% $Pd(OH)_2/C$ (500 mg). The mixture was stirred at room temperature under hydrogen pressure (50 Psi) for 3 h, then was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford very clean amine (*S*)-(−)-**3** (1.40 g, yield: 95%) as a pale yellow liquid. $[\alpha]_D^{25} = -16.5$ (*c* 1.15, $CHCl_3$). R_f: 0.15 (ethyl acetate/cyclohexane = 1/2). ν_{max} (liquid film) 3402, 3338, 2973, 2877, 1617, 1376, 1246, 1152, 1108, 1081, 966, 804. δ_H (400 MHz, $CDCl_3$) 4.00 (m, 2H, H); 3.85 (m, 2H); 3.76 (m, 1H); 2.11 (br s, 2H, NH_2); 1.98 (dd, 1H, *J* = 14.5 and 1.5 Hz); 1.92 (m, 1H); 1.79 (dd, 1H, *J* = 14.5 and 10 Hz); 1.49 (s, 3H, Me); 1.30 (m, 1H). δ_C (100 MHz, $CDCl_3$) 126.5 (q, J_{C-F} = 280 Hz, CF_3), 98.2, 59.7, 59.6, 49.6 (q, J_{C-F} = 29 Hz), 40.3, 25.2, 19.5. δ_F (376 MHz, $CDCl_3$) −81.9. EI-MS (70 eV) *m/z*: 213 (M^+, 1), 198 (40), 101 (100), 73 (40), 43 (90). HR-ESI-MS calculated for $C_8H_{15}F_3NO_2$ $(M+H)^+$: 214.1055, found 214.1050.

4.1.7. (R)-(+)-1,1,1-Trifluoro-3-(2-methyl-1,3-dioxan-2-yl)propan-2-amine (**3**)

Method A: In an hydrogenation vessel (Parr apparatus) was placed a solution of diastereoisomer (2*R*)-(+)-**6b** (2.20 g, 6.94 mmol) in methanol (80 mL), then was added 20% $Pd(OH)_2/C$ (500 mg). The mixture was stirred at room temperature under hydrogen pressure (50 Psi) for 3 h, then was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford very clean amine (*S*)-(+) **3** (1.39 g, yield: 95%) as a pale yellow liquid. $[\alpha]_D^{25} = +16.0$ (*c* 1.30, $CHCl_3$). Other analytical data are identical to those given for its enantiomer (−)-**3** (*vide supra*).

Method B: Following the same procedure but starting from amino-alcohol (2*R*)-**10**, trifluoromethyl amine (*R*)-(+)-**3** was obtained in 80% yield, after silica-gel column chromatography (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = +16.1$ (*c* 1.22, $CHCl_3$). Other analytical data are identical to those given for its enantiomer (−)-**3** (*vide supra*).

4.1.8. (2E)-(+)-Ethyl 3-[(8S, 10R)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]prop-2-enoate (**11**)

To a stirred solution of amine (*R*)-(+)-**3** (1.00 g, 4.7 mmol) in toluene (25 mL) was added ethyl *trans*-4-oxo-2-butenoate 96% (625 μL, 4.9 mmol) and 500 mg of $MgSO_4$. The mixture was stirred at room temperature for 30 min. Intermediate imine solution thus formed was filtered in order to remove the magnesium sulfate. A solution of dry *para*-toluenesulfonic acid (864 mg, 4.5 mmol, previously dried for 3 h under Dean–Stark conditions in 70 mL of toluene) was transferred into the stirred solution of imine at 70 °C and stirred at same temperature for 1 h. The reaction mixture was cooled to room temperature and treated with a saturated $NaHCO_3$ solution (15 mL). The two layers were separated and aqueous layer was extracted with ethyl acetate (3× 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered then concentrated *in vacuo*. Purification by silica gel column chromatography (ethyl acetate/cyclohexane = 1/7) afforded piperidine **(+)-11** (1.03 g, yield: 68%) as a yellow oil. R_f: 0.55 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = +18.5$ (*c* 1.02, $CHCl_3$). ν_{max} (liquid film) 3315, 1715, 1659, 1273, 1173, 1131. δ_H (400 MHz, $CDCl_3$) 6.81 (dd, 1H, *J* = 16 and 6 Hz), 5.95 (dd, 1H, *J* = 16 and 0.5 Hz), 4.10 (q, 2H, *J* = 7 Hz), 3.85 (t, 2H, *J* = 5.5 Hz), 3.80 (t, 2H, *J* = 5.5 Hz), 3.49 (m, 1H), 3.35 (m, 1H), 2.38 (dt, 1H, *J* = 13 and 2.5 Hz, H-7eq), 2.26 (dt, 1H, *J* = 13 and 2.5 Hz, H-11eq), 1.67 (m, 3H), 1.38 (t, 1H, *J* = 13 Hz, H-7ax), 1.23 (t, 1H, *J* = 13 Hz, H-11ax), 1.22 (t, 3H, *J* = 7 Hz). δ_C (100 MHz, $CDCl_3$) 166.2, 148.1, 125.5 (q, J_{C-F} = 277 Hz, CF_3), 121.3, 95.8, 60.5, 59.4, 59.3, 54.7 (q J_{C-F} = 30 Hz), 52.9, 38.1, 31.8, 25.3, 14.2. δ_F (376 MHz, $CDCl_3$) −80.5. EI-MS (70 eV) *m/z*: 323 (M^+, 10), 294 (100), 264 (40), 236 (40), 181 (60), 150 (20), 101 (60), 43 (40). HR-ESI-MS calculated for $C_{14}H_{21}F_3NO_4$ $(M+H)^+$: 324.1423, found 324.1437.

4.1.9. (2E)-(−)-Ethyl 3-[(8R, 10S)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]prop-2-enoate (**11**)

Following the preceding procedure, amine (*S*)-(−)-**3** (1.00 g, 4.7 mmol) and ethyl *trans*-4-oxo-2-butenoate (680 μL, 5.3 mmol), afforded piperidine (−)-**11** (1.00 g, yield: 66%) as a yellow oil. $[\alpha]_D^{25} = -18.5$ (*c* 1.10, $CHCl_3$). Other analytical data are identical to those given for the compound (+)-**11**.

4.1.10. (±)-Ethyl 3[(8S*, 10S*)-10-(trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]propanoate (**13**)

To a stirred solution of compound (±)-**11** (500 mg, 1.5 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ 20% (200 mg). The mixture was stirred at room temperature under hydrogen atmosphere for 1 h then filtered through Celite®. The filtrate was concentrated under reduced pressure then purified by column chromatography on silica gel (ethyl actetate/cyclohexane = 1/3), to afford saturated piperidine

13 (477 mg, yield: 95%) as a colorless liquid. R_f: 0.40 (ethyl acetate/cyclohexane = 1/3). ν_{max} (liquid film) 3321, 2976, 1731, 1266, 1171, 1133, 1088, 1016. δ_H (400 MHz, $CDCl_3$) 3.89 (q, 2H, J = 7 Hz), 3.70 (t, 2H, J = 5.5 Hz), 3.63 (t, 2H, J = 5.5 Hz), 3.12 (m, 1H), 2.60 (m, 1H), 2.22 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.17 (t, 2H, J = 7 Hz), 2.02 (dt, 1H, J = 13 and 2.5 Hz, H-11eq), 1.51 (m, 4H), 1.38 (t, 1H, J = 12.5 Hz, H-7ax), 1.38 (br s, 1H, NH), 1.25 (t, 3H, J = 7 Hz), 1.15 (t, 1H, J = 12 Hz, H-11ax). δ_C (100 MHz, $CDCl_3$) 173.4, 125.5 (q, J_{C-F} = 277 Hz, CF_3), 96.3, 60.5, 59.3, 59.2, 55.0 (q, J_{C-F} = 29 Hz), 51.5, 39.0, 32.1, 31.1, 30.6, 25.3, 14.1. δ_F (376 MHz, $CDCl_3$) −80.4. EI-MS (70 eV) m/z 325 (M^+, 5), 280 (20), 266 (50), 224 (50), 181 (100), 166 (20), 124 (20), 101 (30), 43 (25). HR-ESI-MS calculated for $C_{14}H_{23}F_3NO_4$ $(M+H)^+$: 326.1579, found 326.1569.

4.1.11. (±)-3-[(8S*, 10S*)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]propanoic acid (**12**)

To a stirred solution of ester **13** (56 mg, 0.17 mmol) in methanol (5 mL) was added a 0.3 M NaOH solution (1.8 mL, 0.54 mmol). The mixture was heated at reflux for 1 h then cooled to room temperature before addition of 1 M HCl (2.5 mL). After evaporation of the solvents, the residue was dissolved in the minimum quantity of water and the solution was applied to a column of Dowex® 50 WX 8-100 ion-exchange resin. After elution of water until the eluent was neutral, elution with 1 M NH_4OH followed by concentration to dryness afforded pure amino acid **12** (47 mg, yield: 92%) as a white solid. M.p.: 149 °C. R_f: 0.10 (ethyl acetate). ν_{max} (KBr) 3434, 3240, 2962, 1704, 1276, 1117, 1026, 929. δ_H (400 MHz, D_2O) 4.08–3.92 (m, 5H, H-10), 3.26 (m, 1H), 2.77 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.59 (dt, 1H, J = 13 and 2.5 Hz, H-11eq), 2.49–2.32 (m, 2H), 1.97 (m, 1H), 1.85–1.75 (m, 3H), 1.75 (t, 1H, J = 14 Hz, H-7 ax), 1.52 (dd, 1H, J = 13 and 12.5 Hz, H-11ax). δ_C (100 MHz, D_2O) 180.1, 123.6 (q, J_{C-F} = 277 Hz, CF_3), 95.4, 60.0, 59.9, 54.3 (q, J_{C-F} = 31 Hz), 54.1, 35.5, 32.5, 29.6, 28.6, 24.4.

4.1.12. (2E)-(+)-Ethyl 3-[(7S, 9R)-9-(trifluoromethyl)-1,4-dithia-8-azaspiro[4.5]dec-7-yl]prop-2-enoate (**14**).

To a stirred solution of (+)-**11** (200 mg, 0.62 mmol) in dichloromethane (10 mL), was added dropwise ethanedithiol (260 μL, 2.7 mmol) and $BF_3{\cdot}Et_2O$ (382 μL, 2.7 mmol). The resulting mixture was refluxed until disappearance (TLC monitoring) of the starting material, then cooled to room temperature before addition of an excess of 2 M NaOH. The layers were separated and the aqueous phase was extracted with dichoromethane (3× 30 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, filtered then concentrated *in vacuo* to give, after purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/5), title compound **14** (192 mg, yield: 91%) as a yellow oil. R_f: 0.50 (ethyl acetate/cyclohexane = 1/3). ν_{max} (liquid film) 3310, 2923, 1713, 1658, 1397, 1270, 1172, 1040, 978. δ_H (400 MHz, $CDCl_3$) 6.88 (dd, 1H, J = 16 and 6 Hz), 6.03 (d, 1H, J = 16 Hz), 4.19 (q, 2H, J = 7 Hz), 3.58 (m, 1H), 3.47 (m, 1H), 3.34 (s, 4H), 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-6eq), 2.17 (dt, 1H, J = 13 and 2.5 Hz, H-10eq), 2.0 (dd, 1H, J = 13 and 11.5 Hz, H-6ax), 1.84 (dd, 1H, J = 13 and 11.5 Hz, H-10ax), 1.82 (br s, 1H, NH), 1.30 (t, 3H, J = 7 Hz). δ_C (100 MHz, $CDCl_3$) 166.0, 147.8, 128.0 (q, J_{C-F} = 278 Hz, CF_3); 121.5, 64.4, 60.5, 57.1 (q, J_{C-F} = 29 Hz), 56.0, 46.6, 40.5, 39.4, 38.2, 14.2. EI-MS (70 eV) m/z: 341 (M^+, 20), 312 (20), 280 (30), 248 (100), 199 (25), 163 (20), 112 (15). HR-ESI-MS calculated for $C_{13}H_{19}F_3NO_2S_2$ $(M+H)^+$: 342.0809, found 342.0792.

4.1.13. (+)-Ethyl 3-[(2S, 6R)-6-(trifluoromethyl)piperidin-2-yl]propanoate (**15**)

To a stirred solution of dithioketal (+)-**14** (140 mg, 0.41 mmol) in absolute ethanol (7 mL) was added W2 Raney nickel (*ca.* 500 mg). The resulting suspension was heated at refux for 30 min then cooled to room temperature. The suspension was filtered through Celite® and the filtrate evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and this organic phase was washed with 1 M NaOH, dried on Na_2SO_4 before evaporation of the solvent *in vacuo*. Silica gel column chromatography (ethyl acetate/cyclohexane = 1/5) afforded title compound **15** (83 mg, yield: 80%) as a colorless liquid. R_f: 0.45 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = +12.1$ (c 0.96, $CHCl_3$). ν_{max} (liquid film) 3323, 2940, 1732, 1277, 1175, 1116. δ_H (400 MHz, $CDCl_3$) 4.12 (q, 2H, J = 7 Hz), 3.12 (m, 1H), 2.56 (m, 1H), 2.37 (t, 2H, J = 7.5 Hz), 1.90–1.64 (m, 5H), 1.46 (br s, 1H, NH), 1.28 (m, 2H), 1.22 (t, 3H, J = 7 Hz), 1.07 (m, 1H). δ_C (100 MHz, $CDCl_3$) 173.5, 125.7 (q, J_{C-F} = 277 Hz, CF_3), 60.4, 58.4 (q, J_{C-F} = 29 Hz), 55.5, 31.8, 31.2, 30.5, 24.7, 23.2, 14.1. δ_F (376 MHz, $CDCl_3$) −80.0. EI-MS (70 eV) m/z: 253 (M^+, 1), 208 (30), 152 (100), 96 (10), 55 (10). HR-ESI-MS calculated for $C_{11}H_{19}F_3NO_2$ $(M+H)^+$: 254.1368, found 254.1359.

4.1.14. (−)-3-[(2S, 6R)-6-(Trifluoromethyl)piperidin-2-yl]propanoic acid (**16**)

To a stirred solution of ester (+)-**15** (75 mg, 0.29 mmol) in methanol (5 mL) was added a 0.3 M NaOH solution (1.2 mL, 0.36 mmol). The mixture was heated at reflux for 1 h then cooled to room temperature before addition of 1 M HCl (2 mL). After evaporation of the solvents, the residue was dissolved in the minimum quantity of water and the solution was applied to a column of Dowex® 50 WX 8-100 ion-exchange resin. After elution of water until the eluent was neutral, elution with 1 M NH_4OH followed by concentration to dryness afforded pure amino acid **16** as a white solid. M.p.: 160 °C. $[\alpha]_D^{25} = -14.6$ (c 0.65, MeOH). R_f: 0.10 (ethyl acetate/cyclohexane = 1/1). ν_{max} (KBr) 2500–3500; 1735, 1404, 1263, 1200, 1120. δ_H (400 MHz, D_2O) 3.98 (m, 1H), 3.27 (m, 1H), 2.46 (m, 2H), 2.02 (m, 4H), 1.79 (m, 1H), 1.62 (qd, 1H, J = 13 and 3.5 Hz, H-5′ax), 1.51 (qt, 1H, J = 13 and 3.5 Hz, H-4′ax), 1.35 (qd, 1H, J = 12.5 and 3.5 Hz, H-3′ax). δ_C (100 MHz, D_2O) 176.8, 122.9 (q, J_{C-F} = 278 Hz, CF_3), 58.1, 57.2 (q, J_{C-F} = 32 Hz), 29.4, 27.5, 26.6, 21.3, 20.3. δ_F (376 MHz, D_2O) −75.5. HR-ESI-MS calculated for $C_9H_{15}F_3NO_2$ $(M+H)^+$: 226.1055, found 226.1045.

4.1.15. (±)-(5′S*, 8a′S*)-5′-(Trifluoromethyl)tetrahydro-1′H-spiro[1,3-dioxane-2,7′-indolizin]-3′(3′H)-one (**17**)

To a stirred solution of 2-chloro-1-methylpyridinium iodide (19.7 mg, 0.84 mmol) and triethylamine (21 μL, 0.21 mmol) in anhydrous CH_2Cl_2 (5 mL) was added compound **12** (20 mg, 0.06 mmol). The resulting mixture was stirred for 2 h at room temperature before evaporation of solvent under reduced pressure. The residue was purified by column chromatography (ethyl acetate/cyclohexane = 1/3) to afford title compound **17** (12 mg, yield: 67%) as a white solid. M.p.: 112 °C. R_f: 0.40 (ethyl acetate/cyclohexane = 1/3). ν_{max} (KBr) 2971, 1714, 1407, 1277, 1242, 1135, 1012. δ_H (400 MHz, $CDCl_3$) 4.08 (m, 1H), 3.91 (m, 4H), 3.65 (m, 1H), 2.48–2.14 (m, 6H), 1.80–1.63 (m, 3H), 1.59 (t, 1H, J = 13.5 Hz). δ_C (100 MHz, $CDCl_3$) 173.5, 125.5 (q, J_{C-F} = 280 Hz, CF_3), 96.6, 59.7, 59.6, 54.7, 52.1 (q, J_{C-F} = 33 Hz), 39.3, 32.2, 30.1, 25.1 (2C). δ_F (376 MHz, $CDCl_3$) −72.1. EI-MS (70 eV) m/z: 279 (M^+, 10), 259 (15), 220 (100), 210 (25), 181 (40), 152 (50), 123 (40), 110 (60), 83 (30), 55 (30), 42 (25). HR-ESI-MS calculated for $C_{12}H_{17}F_3NO_3$ $(M+H)^+$: 280.1161, found 280.1169.

4.1.16. (2E)-N-methoxy-N-methyl-4-oxobut-2-enamide (**21**)

To a stirred solution of alcohol **22** [22] (318 mg, 2.19 mmol) in toluene (40 mL) was added MnO_2 (428 mg, 5 mmol). The mixture was heated at 60 °C for 4 h, cooled to room temperature then filtrated through Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel (acetone/dichloromethane = 1/3). Title compound **21** (295 mg, yield: 94%) was obtained as a yellow

oil. R_f: 0.55 (ethyl acetate/cyclohexane = 1/1). ν_{max} (liquid film) 2941, 2830, 2735, 1693, 1652, 1423, 1380, 1180, 1118, 997. δ_H (400 MHz, $CDCl_3$) 9.80 (d, 1H, J = 7 Hz), 7.38 (d, 1H, J = 16 Hz), 7.05 (dd, 1H, J = 16 and 7 Hz), 3.80 (s, 3H), 3.31 (s, 3H). δ_C (100 MHz, $CDCl_3$) 193.6, 164.3, 139.5, 137.7, 62.2, 32.4. EI-MS (70 eV) m/z: 143 (M^+, 5), 114 (70), 83 (70), 61 (10), 55 (100).

4.1.17. (±)-(2E)-N-Methoxy-N-methyl-3-[(7R*,9S*)-9-(trifluoromethyl)-1,4-dithia-8-azaspiro[4.5]dec-7-yl]prop-2-enamide (**27**)

To a stirred solution of triethylamine (112 μL, 1.5 mmol) and 2-chloro-1-methyl pyridinium iodide (112 mg, 0.44 mmol) in dichloromethane (3 mL) was added, in one portion, a solution of *N*,*O*-dimethylhydroxylamine hydrochloride salt (70 mg, 0.71 mmol), triethylamine (112 μL, 1.5 mmol) and crude hydrochloride salt of amino acid **26** (125 mg, 0.35 mmol, prepared by quantitative saponification of ester **14** according to Section 4.1.11, in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 2 h. Evaporation of the solvent, followed by column chromatography (ethyl acetate/cyclohexane 1/1) afforded title compound **27** (100 mg, yield: 79% from **14**) as a yellow oil. R_f: 0.75 (ethyl acetate). ν_{max} (liquid film) 3301, 2929, 1732, 1633, 1424, 1375, 1274, 1244, 1172, 1134, 1046. δ_H (400 MHz, $CDCl_3$) 6.90 (dd, 1H, J = 15.5 and 6 Hz), 6.58 (d, 1H, J = 16 Hz), 3.71 (s, 3H), 3.62 (m, 1H), 3.56 (m, 1H), 3.35 (m, 4H), 3.24 (s, 3H), 2.25 (dt, 1H, J = 13 and 2.5 Hz, H-6eq), 2.17 (dt, 1H, J = 13 and 2.5 Hz, H-10eq), 2.01 (br s, 1H), 2.00 (dd, 1H, J = 13 and 12.5 Hz, H-6ax), 1.91 (dd, 1H, J = 13 and 12.5 Hz, H-10ax). EI-MS (70 eV) m/z: 356 (M^+, 25); 325 (55); 242 (25); 199 (50); 84 (100); 42 (55).

4.1.18. (2E)-(−)-3-[(8R, 10S)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]prop-2-en-1-ol (**29**)

To a cooled (−10 °C) stirred solution of piperidine (−)-**11** (323 mg, 1 mmol) in toluene (10 mL) was added dropwise a 20% solution of diisobutyl aluminum hydride in toluene (1.64 mL, 2.2 mmol). The resulting mixture was stirred at −10 °C for 20 min before addition of methanol (1 mL). After heating to room temperature, the resulting mixture was poured into a mixture of ethyl acetate/saturated sodium chloride (6/1, 70 mL) before extraction with dichloromethane (4× 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvents, followed by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) afforded alcohol (−)-**29** (253 mg, yield: 90%) as a colorless liquid. R_f: 0.20 (ethyl acetate/cyclohexane = 1/1). $[\alpha]_D^{25} = -11.58$ (c 1.07, $CHCl_3$). ν_{max} (liquid film) 3407, 3302, 2962, 1266, 1134, 1020, 974, 862. δ_H (400 MHz, $CDCl_3$) 5.86 (dtd, 1H, J = 15.5, 5.5 and 1 Hz), 5.71 (ddt, 1H, J = 15.5, 7 and 1.5 Hz), 4.14 (dd, 2H, J = 5.5 and 1.5 Hz), 3.91 (t, 2H, J = 5.5 Hz), 3.80 (t, 2H, J = 5.5 Hz), 3.42 (m, 2H), 2.43 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.28 (dt, 1H, J = 13 and 2.5 Hz, H-11eq), 1.74 (Q, 2H, J = 5.5 Hz), 1.57 (br s, 2H), 1.38 (t, 1H, J = 12.5 Hz, H-7ax), 1.23 (dd, 1H, J = 13 and 12 Hz, H-11ax). δ_C (100 MHz, $CDCl_3$) 132.5, 130.7, 125.5 (q, J_{C-F} = 277 Hz, CF_3), 96.1, 62.7, 59.3, 59.2, 54.6 (q J_{C-F} = 29 Hz), 53.7, 38.6, 32.0, 25.3. δ_F (376 MHz, $CDCl_3$) −80.5. EI-MS (70 eV) m/z: 281 (M^+, 5), 263 (40), 250 (30), 222 (100), 181 (95), 150 (40), 101 (80), 69 (50), 43 (60). HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_3$ $(M+H)^+$: 282.1317, found 282.1325.

4.1.19. (2E)-(−)3-[(8R, 10S) -10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]prop-2-enal (**28**)

To a stirred solution of alcohol (−)-**29** (400 mg, 1.4 mmol) in toluene (15 mL) was added MnO_2 (371 mg, 4.27 mmol). The mixture was heated at 60 °C for 3 h, cooled to room temperature, then filtrated through Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by chomatography on silica gel (ethyl acetate/cyclohexane = 1/5). Title compound (−)-**28** (210 mg, yield: 53%) was obtained as a colorless oil. R_f: 0.25 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = -30.1$ (c 1.08, $CHCl_3$). ν_{max} (liquid film) 3306, 2953, 1694, 1275, 1171, 1124, 1088, 974. δ_H (400 MHz, $CDCl_3$) 9.55 (dd, 1H, J = 7.5 and 1.5 Hz), 6.75 (dd, 1H, J = 16 and 6 Hz), 5.95 (m, 1H), 3.93 (m, 4H), 3.72 (m, 1H), 3.45 (m, 1H), 2.52 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.32 (dt, 1H, J = 13 and 2.5 Hz, H-11eq), 1.76 (m, 2H), 1.65 (br s, 1H), 1.45 (t, 1H, J = 13 Hz, H-7ax), 1.35 (t, 1H, J = 13 Hz, H-11ax). δ_C (100 MHz, $CDCl_3$) 193.4, 156.6, 131.7, 125.4 (q, J_{C-F} = 278 Hz, CF_3), 95.7, 59.4 (2C), 54.6 (q, J_{C-F} = 30 Hz), 53.1, 38.3, 31.4, 25.2. δ_F (376 MHz, $CDCl_3$) −80.5. EI-MS (70 eV) m/z: 279 (M, 100), 220 (35), 192 (60), 150 (40), 101 (90), 43 (55). HR-ESI-MS calculated for $C_{12}H_{17}F_3NO_3$ $(M+H)^+$: 280.1166, found 280.1163.

4.1.20. (5′S, 8a′S)-(−)-5′-(Trifluoromethyl)hexahydro-1′H-spiro[1,3-dioxane-2,7′-indolizine] (**30**)

To a stirred solution of aldehyde (−)-**28** (72 mg, 0.26 mmol) in absolute ethanol (5 mL) was added $Pd(OH)_2$/C 20% (100 mg). The mixture was stirred at room temperature under a hydrogen atmosphere for 1 h then filtered through Celite®. The filtrate was concentrated under reduced pressure. Purification on silica gel column (ethyl acetate/cyclohexane = 1/5) afforded title compound (−)-**30** (63 mg, yield: 93%) as a colorless oil. R_f: 0.50 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = -31.6$ (c 1.0, $CHCl_3$). ν_{max} (liquid film) 2966, 2869, 1341, 1272, 1175, 1126, 1017, 927. δ_H (400 MHz, $CDCl_3$) 3.93 (m, 2H), 3.88 (t, 2H, J = 5.5, Hz), 3.23 (m, 1H), 2.83 (m, 1H), 2.44 (br d, 2H, J = 13 Hz, H-6eq and H-7eq), 2.33 (m, 1H), 2.25 (q, 1H, J = 9 Hz), 1.91–1.65 (m, 5H), 1.61 (t, 1H, J = 12.5 Hz, H-6ax), 1.45 (m, 1H), 1.31 (t, 1H, J = 12.5 Hz, H-7ax). δ_C (100 MHz, $CDCl_3$) 125.6 (q, J_{C-F} = 279 Hz, CF_3), 98.8, 60.6, 60.0 (q, J_{C-F} = 29 Hz, C-5), 59.6, 59.2, 51.1, 37.0, 32.8, 29.0, 25.4, 21.5. δ_F (376 MHz, $CDCl_3$) −75.3. EI-MS (70 eV) m/z: 265 (M^+, 10), 206 (80), 196 (50), 164 (20), 96 (100), 41 (15). HR-ESI-MS calculated for $C_{12}H_{19}F_3NO_2$ $(M+H)^+$: 266.1378, found 266.1378.

4.1.21. (3E)-4-[(8R, 10S)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]but-3-en-2-ol (**31**)

To a cooled (−78 °C) stirred solution of aldehyde (−)-**28** (100 mg, 0.36 mmol) in anhydrous THF (5 mL), under argon, was added a 3 M solution of methyl magnesium bromide in diethyl ether (36 μL, 1.1 mmol). The resulting mixture was stirred at −78 °C for 15 min then at 0 °C for 1 h. After warming to room temperature, the reaction mixture was diluted with diethyl ether (5 mL) and a saturated solution of NH_4Cl (3 mL) was added before extraction with diethyl ether (3× 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (ethyl acetate/cyclohexane 1/1) title compound **31** (inseparable 1/1 epimeric mixture, 75 mg, yield: 71%) as a pale yellow oil. R_f: 0.15 (ethyl acetate/cyclohexane = 1/2). δ_H (400 MHz, $CDCl_3$) 5.75 (dd, 1H, J = 15.5 and 6 Hz), 5.65 (dd, 1H, J = 15.5 and 6.5 Hz), 4.30 (Q, 1H, J = 6 Hz), 3.93 (t, 2H, J = 5.5 Hz), 3.89 (t, 2H, J = 5.5 Hz), 3.39 (m, 2H), 2.42 (m, 1H), 2.29 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 1st dia), 2.26 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 2nd dia), 1.74 (Q, 2H, J = 5 Hz), 1.58 (br s, 2H), 1.44 (t, 1H, J = 13 Hz, H-7ax), 1.29 (t, 1H, J = 13 Hz, H-11ax), 1.27 (d, 3H, J = 6.5 Hz). EI-MS (70 eV) m/z: 295 (M^+, 1), 277 (50), 250 (25), 236 (100), 198 (30), 181 (80), 150 (25), 101 (50), 43 (60).

4.1.22. (3E)-(−)-4-[(8R, 10S)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-yl]but-3-en-2-one (**32**)

To a stirred solution of alcohol **31** (100 mg, 0.34 mmol) in toluene (5 mL) was added MnO_2 (88 mg, 1.02 mmol). The resulting suspension was heated at gentle reflux for 5 h, then was cooled to room temperature and filtered through Celite®. The filtrate was concentrated under reduced pressure. Following, a silica

gel-column chromatography (ethyl acetate/cyclohexane = 1/3) afforded title compound **32** (50 mg, yield: 50%) as yellow oil. R_f: 0.44 (ethyl acetate/cyclohexane = 1/1). $[\alpha]_D^{25} = -28.6$ (c 1.4, $CHCl_3$). ν_{max} (liquid film) 3309, 2971, 1680, 1632, 1265, 1173, 1130, 1021, 979. δ_H (400 MHz, $CDCl_3$) 6.70 (dd, 1H, J = 16 and 6 Hz), 6.50 (dd, 1H, J = 16 and 1.5 Hz), 3.95 (t, 2H, J = 5.5 Hz), 3.90 (t, 2H, J = 5.5 Hz), 3.60 (m, 1H), 3.45 (m, 1H), 2.47 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.32 (dt, 1H, J = 13 and 2.5 Hz), 2.28 (s, 3H), 1.75 (m, 2H), 1.65 (br s, 1H), 1.45 (t, 1H, J = 12 Hz, H-7ax), 1.32 (t, 1H, J = 12 Hz, H-11ax). δ_C (100 MHz, $CDCl_3$) 198.3, 146.8, 130.3, 125.4 (q, J_{C-F} = 277 Hz, CF_3), 95.8, 59.4, 59.3, 54.1 (q, J_{C-F} = 29 Hz), 53.2, 38.3, 31.7, 27.2, 25.2. δ_F (376 MHz, $CDCl_3$) −80.5. EI-MS (70 eV) m/z: 293 (M^+, 90), 250 (65), 234 (50), 192 (100), 181 (60), 150 (50), 101 (65), 82 (50), 43 (90). HR-ESI-MS calculated for $C_{13}H_{19}F_3NO_3$ $(M+H)^+$: 294.1317, found 294.1318.

4.1.23. (−)-(3′S, 5′S, 8a′S)-3′-Methyl-5′-(trifluoromethyl)hexahydro-1′H-spiro[1,3-dioxane-2,7′-indolizine] (**33**)

To a stirred solution of enone (−)-**32** (62 mg, 0.21 mmol) in absolute ethanol (5 mL) was added $Pd(OH)_2$/C 20% (100 mg). The mixture was stirred under an hydrogen atmosphere for 1 h then filtered through Celite®. The filtrate was concentrated under reduced pressure. Following, a purification on silica gel column (ethyl acetate/cyclohexane = 1/2) afforded indolizidine (−)-**33** (40 mg, yield: 68%) as a yellow oil. R_f: 0.60 (ethyl acetate/cyclohexane = 1/3). $[\alpha]_D^{25} = -25.6$ (c 0.92, $CHCl_3$). ν_{max} (liquid film) 2960, 1593, 1340, 1272, 1114, 1086, 1039, 997. δ_H (400 MHz, $CDCl_3$) 3.92 (m, 2H), 3.88 (t, 2H, J = 5.5 Hz), 2.95 (m, 2H, H-5), 2.58 (m, 1H), 2.45 (dt, 1H, J = 13 and 2.5 Hz, H-6eq), 2.40 (dt, 1H, J = 13 and 2.5 Hz, H-7eq), 2.06–1.96 (m, 1H), 1.79–1.68 (m, 2H), 1.66–1.58 (m, 2H), 1.55–1.40 (m, 2H), 1.35 (t, 1H, J = 12.5 Hz, H-6ax), 1.11 (d, 3H, J = 6 Hz). δ_C (100 MHz, $CDCl_3$) 125.5 (q, J_{C-F} = 279 Hz, CF_3), 96.7, 60.0, 60.2 (q, J_{C-F} = 27 Hz), 59.6, 59.1, 55.8, 37.4, 34.4, 33.2, 28.9, 25.4, 24.3. δ_F (376 MHz, $CDCl_3$) −73.6. EI-MS (70 eV) m/z: 279 (M^+, 5), 264 (100), 206 (20), 188 (85), 164 (15), 110 (60), 41 (20). HR-ESI-MS calculated for $C_{13}H_{21}F_3NO_2$ $(M+H)^+$: 280.1524, found 280.1524.

4.1.24. (1E)-1-[(8R, 10S)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]hept-1-en-3-ol (**35**)

Compound **35** was prepared from piperidine (−)-**28** following the procedure described above for the synthesis of **31**, using a 2 M solution of n-butylmagnesium chloride in THF (55 μL, 1.1 mmol) instead of a solution of methylmagnesium chloride. Purification by column chromatography on silica gel (ethyl acetate/cyclohexane = 1/1) afforded title compound **35** (inseparable 1/1 epimeric mixture, 82 mg, yield: 68%) as a pale yellow oil. R_f: 0.14 (ethyl acetate/cyclohexane = 1/2). δ_H (400 MHz, $CDCl_3$) 5.68 (m, 2H), 4.08 (m, 1H), 3.93 (t, 2H, J = 5.5 Hz), 3.89 (t, 2H, J = 6 Hz), 3.39 (m, 2H), 2.45 (dt, 0.5H, J = 13 and 2.5 Hz, H-7eq, 1st dia), 2.43 (dt, 0.5H, J = 13 and 2.5 Hz, H-7eq, 2nd dia), 2.28 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 1st dia), 2.23 (dt, 0.5H, J = 13 and 2.5 Hz, H-11eq, 2nd dia), 1.74 (m, 2H), 1.62 (br s, 2H), 1.56–1.22 (m, 8H), 0.90 (t, 3H, J = 7 Hz). EI-MS (70 eV) m/z: 337 (M^+, 21), 319 (30), 278 (100), 250 (40), 198 (40), 181 (95), 150 (25), 123 (30), 101 (50), 41 (50).

4.1.25. (1E)-(−)-1-[(8R, 10S)-10-(Trifluoromethyl)-1,5-dioxa-9-azaspiro[5.5]undec-8-yl]hept-1-en-3-one (**36**)

Compound **36** was prepared from alcohol **35** (290 mg, 0.86 mmol) following the procedure described above for the synthesis of **32**. A column chomatography on silica gel (ethyl acetate/cyclohexane = 1/3) gave title compound (−)-**36** (156 mg, yield: 54%) as a yellow oil. R_f: 0.74 (ethyl acetate/cyclohexane = 1/1). $[\alpha]_D^{25} = -23.5$ (c 1.0, $CHCl_3$). ν_{max} (liquid film) 3310, 2959, 1697, 1633, 1266, 1174, 1130, 1034, 979. δ_C (400 MHz, $CDCl_3$) 6.73 (dd, 1H, J = 16 and 6 Hz), 6.26 (dd, 1H, J = 16 and 1.5 Hz), 3.95 (t, 2H, J = 5.5 Hz), 3.90 (t, 2H, J = 5.5 Hz), 3.58 (m, 1H), 3.44 (m, 1H), 2.55 (t, 2H, J = 7 Hz), 2.46 (dt, 1H, J = 13 and 3 Hz, H-7eq), 2.32 (dt, 1H, J = 13 and 3 Hz, H-11eq), 1.75 (Q, 2H, J = 5.5 Hz), 1.62 (br s, 1H), 1.58 (Q, 2H, J = 7 Hz), 1.42 (t, 1H, J = 12 Hz, H-7ax), 1.38–1.25 (m, 3H), 0.90 (t, 3H, J = 7 Hz). δ_C (100 MHz, $CDCl_3$) 200.5, 145.7, 129.2, 125.4 (q, J_{C-F} = 277 Hz, CF_3), 95.8, 59.7, 59.4, 54.6 (q, J_{C-F} = 29 Hz), 53.2, 40.2, 38.3, 31.8, 26.1, 25.2, 22.3, 13.8. δ_F (376 MHz, $CDCl_3$) −80.5. EI-MS (70 eV) m/z: 335 (M^+, 85), 276 (35), 250 (100), 192 (70), 181 (95), 150 (35), 123 (65), 101 (70), 41 (35). HR-ESI-MS calculated for $C_{16}H_{25}F_3NO_3$ $(M+H)^+$: 336.1787, found 336.1769.

4.1.26. (3′S, 5′S, 8a′S)-(+)-3′-Butyl-5′-(trifluoromethyl)hexahydro-1′H-spiro[1,3-dioxane-2,7′-indolizine] (**34**)

Compound **34** was prepared from piperidine (−)-**36** (100 mg, 0.29 mmol) following the procedure described above for the synthesis of (−)-**33**. The product was purified on silica gel column (ethyl acetate/cyclohexane = 1/2) to afford title compound (+)-**34** (75 mg, yield: 79%) as a yellow oil. R_f: 0.78 (ethyl acetate/cyclohexane = 1/2). $[\alpha]_D^{25} = +1.8$ (c 1.0, $CHCl_3$). ν_{max} (liquid film) 2960, 1468, 1340, 1272, 1165, 1116 (C–O), 1090 (C–O), 1000, 928. δ_H (400 MHz, $CDCl_3$) 3.89 (m, 4H), 3.95 (m, 1H), 2.81 (m, 1H), 2.47 (m, 1H), 2.42 (m, 2H, H-6eq and H-7eq), 1.85–1.10 (m, 14H), 0.87 (t, 3H, J = 7 Hz). δ_C (100 MHz, $CDCl_3$) 125.5 (q, J_{C-F} = 279 Hz, CF_3), 96.7, 62.4, 60.7, 60.1 (q, J_{C-F} = 27 Hz), 59.6, 59.1, 37.6, 37.3, 34.5, 30.6, 29.1, 29.0, 25.4, 22.7, 14.1. δ_F (376 MHz, $CDCl_3$) −73.8. EI-MS (70 eV) m/z: 321 $(M-C_4H_9)^+$, 264 (100), 206 (20), 188 (90), 41 (20). HR-ESI-MS calculated for $C_{16}H_{27}F_3NO_2$ $(M+H)^+$: 322.1994, found 322.1984.

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